REMARKS

Entry of the foregoing, and reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the following remarks.

INFORMATION DISCLOSURE STATEMENT

Applicants thank the Examiner for considering their Second Information Disclosure Statement and returning an initialed copy of Applicants' Second IDS Form PTO-1449.

STATUS OF CLAIMS AND SUPPORT FOR AMENDMENT

Claims 1-17 remain in this application.

Claim 1 has been amended to recite at the end of the claim that said spheroid together with identically defined spheroids is directly tabletable in the form of multiparticulate tablets with no more than approximately 5% of auxiliary substances. This language is fully supported by page 5, lines 3-6 of the specification. Thus, the characterizing portion of Claim 1, not merely the preamble, now reflects the directly tabletable nature of the spheroid, which is indeed an important characteristic of the spheroid itself. Further, the amended language is believed to make clearer how the claimed invention differs from the prior art.

CLAIM REJECTIONS - 35 U.S.C. § 103

Claims 1-17 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the disclosures of Chen et al. US 6,544,556 in view of Criere FR 2, 793,688.

Claim 1, the only independent claim herein, is drawn to a directly tabletable gastroresistant spheroid, which comprises:

(i) a core comprising one or more active principles, directly coated with

(ii) a flexible and deformable film comprising an enteric polymer and a mixture of saturated and/or unsaturated polyglycosylated glycerides whose fatty acids contain at least 8 carbon atoms, and

(iii) a water-dispersible outer layer comprising at least one disintegrant, wherein said spheroid together with identically defined spheroids is directly tabletable in the form of multiparticulate tablets with no more than approximately 5% of auxiliary substances.

It is believed that the Examiner has misunderstood the subject matter to which the claims are directed because the Examiner has said that the claims are drawn to a pharmaceutical formulation comprising a spheroid core with an enteric coating directly applied and an over coating applied to the enteric coating, where the enteric coating comprises a mixture of enteric polymers and surfactants. The Examiner appears to be envisioning applicants' claim as being drawn to a finished drug product for administration in the shape of a sphere, the core of the sphere containing the intended dosage of drug(s) to be administered, the core directly coated with an enteric coating and an overcoating applied over the enteric coating, with particular ingredients (certain polyglycosylated glycerides) in the enteric coat. Such a product is not what is claimed here. Applicants' spheroids are not finished drug products individually; note, for example, page 12, lines 14-15 of the specification which describes the spheroids as advantageously having a diameter of between 0.1 and 2 mm; each of these spheroids has the coatings defined in the claim and is designed to be tableted with other like spheroids to form multiparticulate tablets (a finished dosage form). As noted on page 16, lines 26-30, the multiparticulate tablets disintegrate in solution in less than 60 minutes and restore the individual spheroids, such that the release profile of the tablet and of the spheroids constituting it are virtually equivalent.

The '556 patent describes formulations containing an NSAID and a proton pump inhibitor, in which the proton pump inhibitor is coated with an enteric film, in order to provide an NSAID formulation without the side-effects associated with the NSAID.

The aim of the '556 patent is thus entirely different from the aim of the present invention, which is to provide spheroids which are directly tabletable, i.e., with less than 5% of an auxiliary substance.

The '556 patent describes thus various formulations, notably containing neutral cores coated with the proton pump inhibitor, and then with an enteric coating (col. 9, lines 4-11) and optionally an overcoat (col. 10, lines 27-40).

However, none of the Examples described in the '556 patent corresponds to a formulation containing spheroids as claimed here. indeed, Examples 1 and 3-7 describe tablets comprising an NSAID, the said tablets being coated with the proton pump inhibitor and with an enteric coating. These formulations are thus different from the one of present Claim 1. Applicants' Claim 1 concerns spheroids coated with an enteric coating which are then able to be directly tableted to form a tablet.

Moreover, Examples 2 and 8-12 of the '556 patent relate to capsules comprising an NSAID tablet and spheroids containing the proton inhibitor coated with an enteric coating. A sufficient amount of enteric coated proton pump inhibitor is encapsulated with an NSAID tablet to form NSAID/proton pump inhibitor capsules. Thus, the '556 patent does not describe or suggest spheroids that can be directly tabletable.

Moreover, '556 patent does not even describe the use of polyglycosylated glyceride in the enteric coating while this compound is essential in the framework of the present invention.

The '688 patent document describes gastro-protected granules comprising a proton pump inhibitor as active principle, the granules comprising a coating containing the active principle and an external coating for gastro-protection (enteric coating), each of these coatings containing an hydrophobic substance to increase the stability of the microgranules during storage. Throughout the specification, the '688 document emphasizes the importance of the hydrophobic substances to improve the stability of the formulation during storage. This is noted, for example, in the abstract; on page 2, lines 3-6; on page 5, lines 1-4, 6-10 and 11-15; on page 5, line 28 to page 6, line 4; and in Claim 1. For the gastro-protective layer, a number of substances are mentioned (waxes, oils and their mixtures), but preferably glycerides for example Gelucire®; see page 6, lines 27-31.

It is further noted that the microgranules of the '688 document are intended to be administered in the form of capsules and not of tablets (page 10, lines 18-22), contrary to the spheroids of the invention which are directly tableted, and thus intended to be administered in the form of tablet. Tablets are nowhere mentioned in the '688 document as an ultimate dosage form. Moreover, an intermediate protective coating is preferably inserted between the active coating and the enteric coating (page 7, lines 14-16).

While it is specified, as noted above, that an hydrophobic substance can be contained in the enteric coating, such as glycerides like Gelucire® (page 6, lines 27-31), we emphasize that this substance is used to improve the stability of the microgranules during storage. There is not a scintilla of a suggestion in the '688 document that its microgranules, designed for filling into capsules, might have properties which could allow a direct compression into a multiparticulate tablet as in the present invention. Besides, as already pointed out, the active ingredient in the '688 document is in the coating, not in the core as in applicants' spheroids.

Thus, the combination of the '556 and '688 documents does not describe or lead to spheroids which can be compressed directly. Moreover, the person skilled in the art, who wanted to prepare directly tabletable spheroids, would not be motivated to use the knowledge of the '688 document, in combination with the '556 patent, to prepare the spheroids of the invention.

Indeed, there is nothing in the '688 document to motivate one of ordinary skill to add polyglycosylated glycerides to compositions of the '556 patent to obtain spheroids which are directly tabletable. Both references are silent as to how to design spheroids which are directly tabletable. Silence in a reference is never a proper substitute for an adequate disclosure of facts upon which a conclusion of obviousness can justifiably be based. See *In re Burt and Walter*, 148 USPQ 548 (1966) CCPA.

RESPONSE TO ARGUMENTS

In the Examiner's response to applicants' arguments on page 4 of the Official action, the Examiner claims that the '556 document discloses "seeds" which are coated and compressed to form a tablet. Applicants do not know what "seeds" the

Examiner refers to. There are granules described, for example in Examples 1 and 2, but these are extended release granules of the NSAID. These extended release granules are compressed into tablets, which are spray coated with a suspension of omeprazole. The omeprazole-coated tablet is then enteric coated, then color coated. There are multiparticulate substrates described, where particles of enteric-coated proton-pump inhibitor are mixed with NSAID particles, or inert beads are coated with proton pump inhibitor overcoated with an enteric coating and thereafter coated with NSAID; or one population of beads is coated with proton pump inhibitor and thereafter enteric coated, while the other population of beads is coated with NSAID; thereafter appropriate amounts of each of these different populations can be incorporated into tablets or into gelatin capsules. None of these possibilities describes or suggests the directly tabletable gastroresistant spheroid of applicants' claims. Moreover, the enteric-coated substrates of the '556 document are mixed with tablet excipients (column 10, lines 41-44), which is contrary to the aims of the present invention.

CONCLUSION

In view of the foregoing, it is believed that the record 35 U.S.C. § 103 rejection has been overcome. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited.

Respectfully submitted,

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